Usefulness of dermoscopy/dermatoscopy to improve the clinical and histopathologic diagnosis of skin cancers

Yélamos, Oriol ; Braun, Ralph P ; Liopyris, Konstantinos ; Wolner, Zachary J ; Kerl, Katrin ; Gerami, Pedram ; Marghoob, Ashfaq A

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Oriol Yélamos, MD, Ralph P. Braun, MD, Konstantinos Liopyris, MD, Zachary J. Wolner, BA, Katrin Kerl, MD, Pedram Gerami, MD, Ashfaq A. Marghoob, MD

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Authors: Oriol Yélamos, MD;[1,2] Ralph P Braun, MD[3] Konstantinos Liopyris, MD; [1] Zachary J Wolner, BA; [1] Katrin Kerl, MD; [3] Pedram Gerami, MD; [4] Ashfaq A Marghoob, MD; [1,5]

-**Institution**: [1]Dermatology Service, Memorial Sloan Kettering Cancer Center, New York, NY;
[2] Dermatology Department, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain;
[3]Department of Dermatology, University Hospital Zürich, Switzerland;
[4]Department of Dermatology, Feinberg School of Medicine, The Robert H. Lurie Cancer Center, Northwestern University, Chicago, IL, USA
[5]Dermatology Service, Memorial Sloan Kettering Cancer Center, Hauppauge, NY

Corresponding author:

Oriol Yélamos, MD
oyelamos@gmail.com

Memorial Sloan Kettering Cancer Center
Dermatology Service
16 East 60th St. 4th Floor
New York, New York, 10022
646-888-6269

Dermatology Department
Hospital Clínic
Universitat de Barcelona
Villarroel 170, 08036 Barcelona, Spain

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ABSTRACT

Multiple studies have shown that dermoscopy increases the sensitivity and specificity for the detection of skin cancers compared to naked-eye examination. Dermoscopy can also lead to the detection of thinner and smaller cancers. Furthermore, dermoscopy leads to more precise selection of lesions requiring excision. In essence, dermoscopy helps clinicians differentiate benign from malignant lesions through the presence or absence of specific dermoscopic structures. Therefore, since most dermoscopic structures have direct histopathologic correlates, dermoscopy can allow the prediction of certain histologic findings present in skin cancers, thus helping select management and treatment options for select types of skin cancers. Visualizing dermoscopic structures in the ex vivo specimens can also be beneficial. It can improve the histologic diagnostic accuracy by targeted step-sectioning in areas of concern, which can be marked by the clinician before sending the specimen to the pathologist, or by the pathologist on the excised specimen in the laboratory. In addition, ex vivo dermoscopy can also be used to select tumor areas with genetic importance since some dermoscopic structures have been related to mutations with theragnostic relevance. In the second article of this continuing medical education series we review the impact of dermoscopy on the diagnostic accuracy of skin cancer, how can dermoscopy affect the histopathologic examination, and which dermoscopic features may be more relevant in terms of histological and genetic prediction.

INTRODUCTION

Dermoscopy has shown to increase the sensitivity for detecting skin cancers compared to naked-eye examination (NEE), and this increase is not occurring at the expense of a lower specificity.[1] In essence, dermoscopy leads to the biopsy of a more selective group of lesions and this is reflected in a reduction in the number of benign lesions biopsied for every skin cancer found.[1-3] Dermoscopy helps distinguishing benign from malignant lesions by revealing structures and patterns not visible with the NEE. Since these structures have direct histopathologic correlates (continuing medical education [CME] part 1), clinicians can more precisely predict histologic findings. In addition, visualizing dermoscopic structures in the ex vivo biopsy specimens can also be beneficial. This is particularly relevant when grossing skin cancers such as melanomas since there may be variability in tumor thickness across the tumoral area. In addition, some melanomas may be focally present within a nevus and in this scenario the correct diagnosis will be contingent upon sectioning the tissue in the appropriate plane. In fact, dermoscopy can improve grossing since only about 0.1% of a 4 mm specimen actually gets presented to the pathologist on a glass slide.[4]

Multiple methods aimed at targeting the areas to step-section have been proposed by clinicians and pathologists. Clinicians can provide descriptions or pictures of the lesion to the pathologist, or can mark the area directly on the specimenby suture, ink or punch scoring before sending it to the laboratory.[5-9] [4] Conversely, this marking can also be done in the laboratory by the pathologist or histo-technician since most dermoscopic structures can be identified on formalin fixed tissue,[10] in a process called ex vivo dermoscopy (EVD) (figure 1).[11] Dermoscopy-guided sectioning may reduce the number of slides necessary to render a correct

diagnosis and this can impact cost containment in a positive manner. In addition, studies have shown that select dermoscopic structures can predict a higher degree of atypia, genetic mutations, or certain histologic subtypes when evaluating lesions suspicious for skin cancers.[4, 12-15] Therefore, dermoscopy-guided sectioning offers an exciting opportunity for research by selecting different samples for biobanks, and allowing the detection of genetic mutations with theragnostic implications.

USE OF DERMOSCOPY TO IMPROVE THE CLINICAL DIAGNOSTIC ACCURACY FOR SKIN CANCER DETECTION

Key notes

- Dermoscopy increases the sensitivity for skin cancer detection and lowers the benign to malignant biopsy ratio.
- Limitations of dermoscopy include the learning curve and the occasional nonconformity of skin cancers to defined diagnostic criteria.
- Ultimately, the decision to biopsy a lesion requires the integration of multiple parameters including clinical information, morphologic analysis, and comparative and pattern analysis.

Advantages of dermoscopy

Since melanoma can become an aggressive tumor, maintaining a high sensitivity remains paramount and lesions clinically suspicious for malignancy should be excised. Some have suggested that it is justifiable to biopsy over 100 benign lesions in order to detect a single melanoma at an early stage.[16] This aggressive approach with the aim of maintaining a high sensitivity, fails to acknowledge the harmful consequences from having such a low specificity (i.e., scarring, pain, would infection, patient fear/anxiety) and driving up costs of health care.

Multiple meta-analyses have shown that dermoscopy improves user diagnostic accuracy for diagnosing skin cancers.[1, 17, 18] In fact, dermoscopy enables the detection of melanomas with a sensitivity that is significantly higher than the NEE (90% vs 71%).[1] This is in part due to the misclassification of approximately 40% of melanomas as benign when using only the clinical

ABCDE rule.[19] Dermoscopy also has a higher specificity compared to NEE (90% vs 81%).[1] This results in fewer biopsies/excisions necessary to find a skin cancer (4-5:1 with dermoscopy vs 12-15:1 with NEE alone[2, 24]). One would think that reducing the benign to malignant biopsy ratio (BMR) may be at the cost of detecting more advanced cancers. However, dermoscopy in fact detects skin cancers at an earlier stage compared to NEE.[3, 25-28] Thus, because dermoscopy has a high sensitivity for diagnosing skin cancers, it decreases the number of unnecessary biopsies, it identifies cancers earlier, and it results in a cost-effective cancer screening strategy.[29, 30]

Limitations of dermoscopy

As with any diagnostic tool, dermoscopy requires training During the training and learning phase the clinicians tend to increase their sensitivity but lower their specificity. In fact, during the first year after learning dermoscopy, generally the BMR increases.[18, 34] However, after gaining some experience, the clinician's specificity also increases and this eventuates into an improved BMR compared to pre-dermoscopy use and NEE.[34]

It is important to highlight that dermoscopy should not be used without clinical history and clinical findings. The history and clinical features such as degree of firmness, and elevation are important pieces of information that need to be placed in context with the dermoscopic morphology. The final decision on whether to biopsy or not requires the integration of analytical data (i.e., clinical ABCDE, dermoscopic features), comparative reasoning (i.e., is the lesion new or changing compared to previous images), differential recognition (i.e., ugly duckling, single vs multiple lesions), pattern recognition or gestalt, patient history (i.e., age, gender, comorbidities), and "gut feeling".[35] This is important to appreciate since some skin cancers may lack specific

dermoscopic features, making them impossible to diagnose based purely on dermoscopic morphology. In addition, dermoscopic features and patterns may vary based on age, skin type, location, and extent of sun damage and this information also needs to be placed in context when interpreting dermoscopy. Despite these limitations, there is not a single study that has shown that dermoscopists perform worse as compared to non-dermoscopists.

USING DERMOSCOPY TO IMPROVE HISTOLOGICAL ANALYSIS

Key notes

- Dermoscopy can inform the pathologist on how best to process and section the tissue. This dermoscopic information can be provided to the pathologist via dermoscopic images or descriptions, and by the clinician marking the area of most concern before submitting the specimen to the laboratory.
- Since most dermoscopic features are visible after formalin fixation, dermoscopy can be used to guide step sectioning in the laboratory in a technique called ex vivo dermoscopy.
- Marking the specimen in vivo or ex vivo using dermoscopy improves the histological diagnostic accuracy and potentially reduces the costs of histologic processing.

The role of the clinician

Dermoscopy is widely used by dermatologists and non-dermatologists,[31, 41] who are increasingly sampling a higher proportion of complex and histological equivocal lesions. For such lesions the clinical information may greatly help the pathologist in rendering the most accurate diagnosis. Clinicians can provide pathologists with clinical images, dermoscopic

images, dermoscopic descriptions, or may mark areas of interest before sending the specimen to the pathology laboratory.[6-8] However, dermoscopy images and descriptions are only useful if sent to dermatopathologists who understand the importance of clinical-dermoscopy-histopathology correlations and who have acquired at least some knowledge about dermoscopy and their association with disease. For specimens sent to dermatopathologists who have little or no knowledge about dermoscopy, the clinician may want to consider marking the area of interest or bisecting the specimen in the plane of interest so as to insure that the area of clinical concern does in fact get sectioned. While these strategies have shown to improve the diagnostic accuracy of pathologists, currently they are rarely employed outside specialized cancer centers.[42] As the importance of clinical-dermoscopy-pathology correlation becomes more widely appreciated, it is likely that the aforementioned methods will be more widely adopted.

Benefits of including dermoscopic information and/or images as part of the pathology requisition form:

As part of the pathology request form, an increasing number of clinicians are starting to add drawings, pictures or dermoscopic descriptors to the clinical information of lesions being submitted. This added information improves the diagnostic accuracy of histological analysis[43] as it directs the pathologic analysis and elicits a more careful examination of sections.[44] Ideally, pathologists should have access to clinical and dermoscopic images of complex melanocytic lesions in order to visually assess the areas of highest concern and determine orientation of step sectioning. Contrary to a common misconception, access to additional information prior to histopathologic review is not associated with diagnostic bias and actually may be helpful,[5] even increasing the histologic interobserver agreement.[9]

Advantages for the pathologist of highlighting the area/s of clinical concern within excised lesion:

Before sending a specimen, clinicians have the opportunity to mark areas that display dermoscopic features that may have significance for the pathologist during the histopathological analysis. Clinicians can mark the specimen in multiple ways including using ink or nail varnish, placing a suture in the area of interest, scoring the area with a scalpel or a micropunch, or bisecting the specimen themselves.[4, 6-8] Irrespective of the method, the mark left by the clinician may help identify small select areas that may have been otherwise missed during the conventional step sectioning procedure (figure 2).[4] However, clinicians must be cautioned not to damage the scored tissue to such an extent as to compromise histopathologic analysis.[4]

The role of the pathologist

Dermatopathologists routinely evaluate full-thickness skin sections in the vertical plane of a small percentage of the entire specimens volume, whereas dermoscopists evaluate the entire lesion in the horizontal plane but only to a maximum depth of the papillary dermis.[45] Therefore, both techniques are complementary and can be used in the laboratory to improve grossing. Towards this goal, pathologists need to acquire knowledge of the dermoscopy terminology and histology correlates, and dermoscopists need to acquire knowledge of histopathology (CME part 1).

Benefits of examining the ex vivo dermoscopy before step-sectioning

Dermoscopy is a diagnostic tool meant to be used in vivo directly on the patient's skin. However, dermoscopy can also be used on excised tissue because most dermoscopic features are visible even after formalin fixation.[10, 11] This technique is called ex vivo dermoscopy (EVD),[11] and can help guide specimen grossing. As previously indicated (CME part 1), the colors and structures seen on dermoscopy have histopathologic correlates, which may have diagnostic and prognostic significance. For example, when grossing a pigmented melanoma, sections containing scarlike depigmentation or peppering on dermoscopy may underestimate the tumor thickness as they correspond to regression. Conversely, blue-gray areas indicate deep dermal melanocytes and thus this area will likely provide the most accurate indication of maximum tumor thickness.[46, 47] EVD can also be useful to the pathologist when little or no clinical information is provided in the requisition form. In this scenario, reviewing the submitted specimen with a dermatoscope before grossing the lesion has shown to improve the diagnosis of ambiguous melanocytic and non-melanocytic lesions.[48-50] Haspeslagh et al. found that EVD improved the detection of positive margins in keratinocyte carcinomas from ~8% to ~13%. In melanocytic lesions, this technique lead to the detection of a higher degree of atypia, ulceration, and higher mitotic rates.[50] In addition, Cabete et al. found that EVD elicited a change in the final diagnosis in ~14% of the studied cases, and EVD helped in the detection of melanomas missed with conventional step sectioning and improved the staging of melanomas.[49] In addition, EVD has shown to decrease the diagnostic turnaround time[50], a finding that indicates EVD can potentially optimize step-sectioning and reduce the costs of histopathologic processing.

EVD has some differences compared to conventional dermoscopy. While EVD clearly identifies structures containing pigment such as network, globules or streaks,[10, 11] some structures

are less conspicuous. In EVD, there are more structureless areas and a decrease in the focus sharpness.[10, 11, 48] Furthermore, after fixation some colors may appear enhanced (blue, brown, white), while others colors such as red may be less conspicuous due to a poor or absent visualization of blood vessels and degradation of hemoglobin after excision.[10, 11, 51] This makes EVD challenging in amelanotic lesions. Another way to evaluate the dermoscopic features of excised specimens can be through photographs of the dermoscopic image. A dermatoscope can be attached to a camera[50] or simply attached to a smartphone (figure 1). This results in a cleaner and safer method to evaluate lesions, and provides an easy way to document the findings for future clinical, research, or academic purposes. EVD has a more important role in medium-to-large complex pigmented lesions or in wide excisions containing focal pigmented areas than on tiny specimens.[11] Regarding larger lesions, the same way clinicians may mark the area of concern, pathologists or histo-technicians can also mark the specimen in order to identify a given area under the microscope.[52] In fact, it has been suggested that the marking of the specimen should be performed in the laboratory to minimize tissue loss or destruction.[50, 52]

In the era of targeted therapies, EVD also has exciting potential in research. Several dermoscopic structures have been correlated with select genetic mutations (see below). Therefore, EVD can be used as a tool to gross specimens and select areas which can later be tested for mutations, or stored for future studies in biobanks. The dermoscopic image could then serve as an en face map of the clones present within a given lesion.[53]

DERMOSCOPIC FEATURES WITH SPECIAL RELEVANCE FOR THE CLINICIAN AND THE PATHOLOGIST

Key points

- Several dermoscopic features are highly specific for melanoma and are called melanoma-specific structures.
- Select dermoscopic findings can predict the presence of aggressive melanomas as well as the presence of genetic mutations.
- Dermoscopy can predict the indolent vs. aggressive subtypes of keratinocyte carcinomas and may help triage lesions.
- Although relatively specific, the structures suggestive for melanocytic lesions can be encountered in non-melanocytic lesions and this may explain the discordance between the clinical/dermoscopic and the final histopathological diagnosis of many cases.

Dermoscopic features with special relevance present in melanocytic lesions

1. Melanoma-specific structures

Several dermoscopic features have been associated with a high odds ratio for melanoma when encountered in melanocytic lesions. These structures are collectively known as melanoma-specific structures. They include atypical pigment network, angulated lines, irregular streaks, negative pigment network, shiny white streaks, irregular dots and globules, irregular blotch, blue-white veil, regression structures (peppering and scarlike depigmentation), and polymorphous vessels. These features, which have well-established histopathological correlates

(CME part 1), are summarized in table I and shown in figure 3. We have described these features according to the 2016 International Dermoscopy Consensus on dermoscopic terminology.[54, 55]

2. Dermoscopic structures associated with prognostic and therapeutic implications

A few dermoscopic structures have been shown to have clinical and prognostic significance with structures associated with melanoma arising in a nevus,[50,62] dermal invasion,[56] Breslow >0.75mm,[47, 57-59] mitotic activity,[60, 61] or presence of lymph node metastases.[62] Other dermoscopic features may also be relevant for therapeutic purposes as they are associated with genetic mutations targetable by specific therapies.[12, 13, 15, 63] These findings are summarized in table II.

Dermoscopic predictors of basal cell carcinoma subtype

Dermoscopy can be used to predict the most common subtypes of basal cell carcinomas (BCC): nodular and superficial. Lallas et al developed an algorithm in which the most relevant discriminator between superficial and non-superficial BCC was the presence of blue-ovoid nests (in the non-superficial subtypes).[64] They also found arborizing vessels and ulceration to be associated with non-superficial BCC. Conversely, the presence of leaflike areas and serpentine vessels were associated with superficial BCC. Recently, Ahnlide et al. demonstrated that the presence of multiple small erosions in a flat lesion is predictive of superficial BCC in fair-skinned individuals.[14]

Thus, the findings more commonly associated with superficial BCC are serpentine vessels, multiple small erosions, flat surface and leaflike/spokewheel areas. The presence of

blue-ovoid nest, ulceration and arborizing vessels are more common in nodular BCC (figure 4, table III). This distinction can determine management since superficial BCC can potentially be treated non-surgically; streamlining the diagnostic and therapeutic process through a reduction in diagnostic biopsies. However, caution is advised since small foci of invasion cannot be excluded dermoscopically, and therefore other techniques such as reflectance confocal microscopy or optical coherence tomography can be used to identify deep tumor components.[65-68] Interestingly, some dermoscopic findings have been described as therapeutic predictors. For example, the presence of ulceration in a non-treated BCC has been described to predict a good response to imquimod, regardless of subtype.[69]

Dermoscopic predictors of the squamous cell carcinoma spectrum

The lesions included in the squamous cell carcinoma (SCC) spectrum share many dermoscopic features such as scale, rosettes and vessels. However, other dermoscopic features can aid in differentiating actinic keratosis, Bowen disease, well-differentiated SCC, and invasive SCC. The findings are summarized in table IV and shown in figure 5.

CONCLUSION

In this CME series we have reviewed dermoscopic structures with their histopathology correlates and have shown that there exists an overlap between dermoscopy and histopathology. However, dermoscopy and histopathology are not equivalent. Histopathology holds an advantage over dermoscopy in that it evaluates vertical sections of tissue, which allows for the assessment of the full depth of the lesion from scanning magnification to cellular-level magnification. In addition, since histopathology is performed on paraffin-embedded tissue, it permits the use of immunohistochemical and molecular techniques to assist in diagnosis, which clearly cannot be done with dermoscopy. Conversely, unlike histology which evaluates less than 1% of the entire volume of the tumor, dermoscopy evaluates the entire surface area of the lesion in the horizontal plane, but only to the depth of the papillary dermis and not at cellular level resolution. The ability to evaluate the lesion in the horizontal plane permits the identification of certain diagnostically important structures, such as streaks, that are not commonly seen on vertical section histopathology. In addition, dermoscopy has the advantage of allowing the observer to identify colors, which may prove important in rendering a diagnosis. Other advantages of dermoscopy include the ability to evaluate the context of lesions on the skin and to monitor lesions over time to determine their biology and dynamics.

Dermoscopy is an ideal tool to enhance the diagnosis of skin cancer and in fact has a high sensitivity for the diagnosis of skin cancers while retaining a high specificity, resulting in a low BMR. In addition, dermoscopy can identify areas within a tumor that have prognostic relevance for the pathologist when performing step sectioning. Therefore, dermoscopy can improve histologic diagnostic accuracy, reduce costs of histologic processing, and offer research

355 opportunities through informed sampling of specimens for genetic testing. However, an adequate
356 knowledge of dermoscopy is required since exceptions occur. Nevertheless, dermoscopy can be a
357 bridge between clinicians and pathologists that strengthens the clinical-pathological correlation.

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569

570 -**ABBREVIATIONS AND ACRONYMS:**

571 AK – Actinic Keratosis

572 BCC – Basal Cell Carcinoma

573 BMR – Benign to Malignant Ratio

574 CME - Continuing Medical Education

575 EVD – Ex Vivo Dermoscopy

576 NEE – Naked-Eye Examination

577 RCM – Reflectance Confocal Microscopy

578 SCC - Squamous Cell Carcinoma

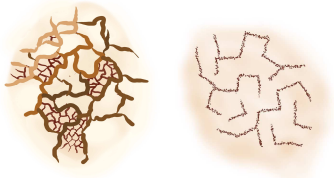
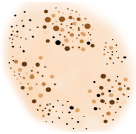
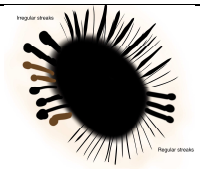
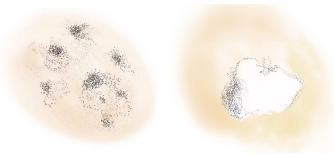
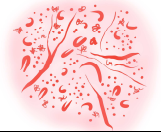
579

ACKNOWLEDGEMENTS

We would like to thank Dr Mary Le for her assistance in acquiring images for this CME series.

582 **TABLES:**

583 **Table I.** Dermoscopic melanoma-specific structures and its odds ratio for melanoma

Schematic illustration	Metaphoric term	Description	Odds ratio for melanoma
	Atypical pigment network and angulated lines	Network with increased variability in the color, thickness, distribution and/or spacing of the lines. When angulated, typically they show gray color	2-9[22, 70-73]
	Negative pigment network	Serpiginous interconnecting broadened hypopigmented lines that surround elongated and curvilinear globules	1.4-1.8[71, 74]
	Irregular dots/globules	Clods with variability in color, size, shape, or spacing and distributed in an asymmetric fashion	1.7-4.8[22, 70, 75]
	Irregular streaks (pseudopods and radial streaming)	Radial lines with bulbous projections (pseudopods) or without (radial streaming) irregularly distributed	1.5-5.8[22, 70-72, 75]
	Granularity / peppering and scarlike depigmentation	Granularity: blue-gray dots Scarlike depigmentation: white area lighter than surrounding skin devoid of vessels and shiny white structures	2-18.3[70-72, 75]
	Blue-whitish veil	Homogenous white blue area overlying a raised area	1.74-13[70-72, 75]
	Shiny white streaks	Short white lines oriented parallel and orthogonal to each other (only seen in polarized dermoscopy)	2.5- 9.7[71, 76]
	Irregular blotch	One off-centered blotch or multiple blotches	1.88-4.1[22, 70-72]
	Polymorphous vessels	Simultaneous presence of multiple types of vessels	2.0-3.04[22, 71, 72]

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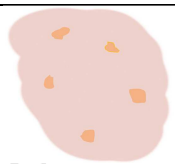
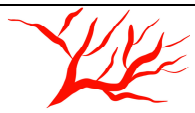
586 **Table II.** Dermoscopic structures which have been shown to be predictors of histologic and
587 genetic alterations when present in melanocytic lesions:

Histologic/genetic association		**Dermoscopic predictors**
Melanoma arising in a nevus[50,62]		Negative pigment network
Breslow depth >0.75 mm[47, 57-59]		Blue-whitish veil
		Atypical Vessels
		Abrupt cutoff
		More than 4 colors
		Streaks
		Milky red areas
		More than 2 dermoscopic structures
Dermal invasion[56]		Shiny white streaks
Mitosis in thin (<1 mm) melanoma[60]		Black color
		Peripheral streaks
Mitosis and ulceration[61]		Shiny white streaks
		Blue-whitish veil
		Milky-red areas
Positive sentinel lymph node[62]		Blotch
		Ulceration without a pigmented network
Genetic mutations	MAPK mutations (*BRAF*, *NRAS*)[13]	Peppering/granularity
	BRAF-mutated melanomas[12, 15]	Irregular peripheral streaks
		Ulceration
		Blue-whitish veil
	BRAF wild-type melanomas[12]	Dotted vessels
	KIT mutations[63]	Dark homogeneous streaks

588 **Table III.** Dermoscopic structures associated with basal cell carcinoma subtypes:

Basal cell carcinoma subtype	Dermoscopic predictors	Schematic
Superficial basal cell carcinoma[14, 64]	Flat surface	
	Multiple small erosions	
	Serpentine vessels	
	Leaflike structures	
Non-superficial basal cell carcinoma[64]	Blue ovoid nest	
	Arborizing vessels	
	Ulceration	

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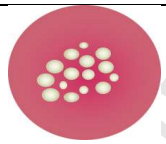
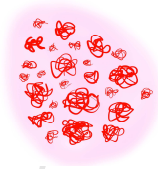
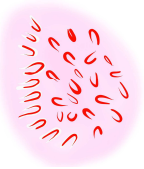
592 **Table IV.** Dermoscopic structures associated with subtypes of squamous cell carcinoma
593 subtypes.

Histologic subtype	Dermoscopic predictors	Schematic
Actinic keratosis[77]	Strawberry pattern	
Bowen disease[78]	Glomerular vessels	
	Dark dots/globules or round circles in linear arrangement	
Well-differentiated squamous cell carcinoma[77, 79]	White circles	
	Looped vessels	
Poorly-differentiated squamous cell carcinoma[80]	Vessels in >50% of the tumor surface	
	Diffuse arrangement of vessels	
	Bleeding	

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-FIGURE LEGENDS:

Fig 1. Evaluation of dermoscopic features on a formalin-fixed specimen (ex vivo dermoscopy) using a smartphone attached to a dermatoscope.

Fig 2. Pigmented lesion showing an overall reticular pattern with an off-centered area of atypical blue and gray dots and globules (A, upper circle) and an area with scarlike depigmentation (A, lower circle). Histopathologically, the area with atypical globules revealed a higher degree of atypia (B) as opposed to the area depicting scarlike depigmentation on dermoscopy (C). Thus, dermoscopy can be useful in identifying the areas with higher degree of atypia.

Fig 3. Dermoscopic images showing multiple melanoma-specific structures **A,** Melanoma arising in a nevus presenting with negative network (arrow) and irregular globules (arrowhead) **B,** Lentigo maligna depicting angulated lines (arrows) **C,** Invasive melanoma showing blue-whitish veil (asterisk), streaks (arrow) and irregular globules (arrowhead). **D,** Regressed melanoma presenting with atypical network (arrowheads), scarlike depigmentation and peppering (asterisk) and an irregular blotch (arrow).

Fig 4. Dermoscopic images showing dermoscopic features associated with different basal cell subtypes **A,** Superficial basal cell carcinoma presenting with an erosion (asterisk), serpentine vessels (arrowhead) and leaflike areas (arrow) **B,** Nodular basal cell carcinoma presenting with an ulcer (asterisk), arborizing vessels (arrowhead) and blue ovoid nests (arrow).

Fig 5. Dermoscopic images showing dermoscopic features associated with different squamous cell subtypes **A,** Actinic keratosis presenting with an overall strawberry pattern **B,** Well-differentiated squamous cell carcinoma presenting with central keratin plug (asterisk), looped vessels (arrow) and white circles (arrowhead) **C,** In situ squamous cell carcinoma depicting multiple linear black dots (arrowhead) **D,** Poorly-differentiated squamous cell carcinoma depicting diffuse polymorphous vessels (arrowheads) and scale (asterisk).